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INDICATORS OF GENERAL IMMUNITY IN PATIENTS WITH IATROGENIC MAXILLARY SINUSITIS

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The dependence of the pathogenesis of chronic maxillary sinusitis on the factors influencing the formation of the maxillary course of the disease was studied according to the indicators of general immunity. The pathogenesis of the drug-induced iatrogenic sinusitis is due not to the nature of dental manipulations, and long-term use of drugs. In other forms of iatrogenic sinusitis of dental origin, the severity of the disease directly depends on the nature and extent of dental intervention. For the drug form, the acute phase of inflammation and the secondary type of immune response are more pronounced in relation to other studied iatrogenic subgroups against the background of low induced activity of immune cells: T-cell parameters (CD 3+, CD56+) – 5.8 %; average CIC – 82.4±4.45 OU ($p<0.05$); IgG – 15.27±3.47 g/l, $p<0.05$; induced activity of immune cells – 233.2±27.5 OU. In the traumatic form of iatrogenic maxillary sinusitis is expressed primary sensitization: high value of IgE – 226.16±70.4 IU/ml, $p<0.05$ Relatively favorable immunological course is observed in infectious-allergic and mixed forms of iatrogenic maxillary sinusitis.

Key words: general immunity, maxillary sinusitis, foreign body, perforation, differential diagnostics.

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ПОКАЗНИКИ ЗАГАЛЬНОГО ІМУНІТЕТУ ПАЦІЄНТІВ З ЯТРОГЕННИМ ВЕРХНЬОЩЕЛЕПНИМ СИНУСИТОМ

За показниками загального імунітету досліджено залежність патогенезу хронічного верхньощелепного синуситу від факторів, що впливають на формування верхньощелепного перебігу захворювання. Патогенез медикаментозній формі ятрогенного синуситу обумовлені не характером стоматологічних маніпуляцій, а тривалим прийомом лікарських препаратів. При інших формах ятрогенного синуситу стоматогенного походження тяжкість хвороби безпосередньо залежить від характеру та обсягу стоматологічного втручання. Для медикаментозної (лікарської) форми відносно до інших досліджуваних ятрогенних підгруп більше виражена гостра фаза запалення та вторинний тип імунної відповіді на тлі низької індукованої активності імунних клітин: показники Т-клітин (CD 3+, CD56+) 5,8 %; середніх ЦІК – 82,4±4,45 у.о. ($p<0,05$); IgG – 15,27±3,47 г/л ($p<0,05$); індукована активність імунних клітин – 233,2±27,5 у.о.. При травматичній формі ятрогенного верхньощелепного синуситу виражена первинна сенсибілізація: високе значення IgE – 226,16±70,4 МО/мл, ($p<0,05$). Відносно сприятливий імунологічний перебіг спостерігається при інфекційно-алергічній та змішаній формах ятрогенного верхньощелепного синуситу.

Ключові слова: загальний імунітет, гайморит, сторонє тіло, перфорація, диференціальна діагностика.

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According to publications in recent years, up to 30–40 % of cases of chronic sinusitis are caused by non-infectious, dental factors [4, 11]. The close anatomical location of the upper teeth to the maxillary sinus contributes to the spread of periapical or periodontal odontogenic infection into it. Sinusitis can develop with osteomyelitis of the upper jaw, radicular cysts, after mechanical damage to the sinus mucosa during root canal treatment, overflow of root canals with endodontic material that protrudes into the maxillary sinus, after manipulations to increase bone volume at the bottom of the sinus, in the presence of oroanthral fistula after tooth extraction [5, 13]. Chronic maxillary sinusitis can develop as a result of damage to the sinus by periapical infection of the posterior teeth of the upper jaw, violation of the integrity of its membrane due to iatrogenic causes, for example, trauma during manipulation of maxillofacial surgery, after implantation, endodontic manipulations. Diagnosis of inflammatory processes in the maxillary sinus with the establishment of stomatogenic and iatrogenic causes of the disease is important for successful treatment [15].

Diseases of the maxillary sinus by their nature can be classified as: congenital (aplasia and hypoplasia); neoplastic (benign or malignant); dental conditions (benign dental tumor, odontogenic cyst, or periapical inflammatory lesion); bone injury (ossifying fibroma); traumatic bone injury; iatrogenic (associated with previous interventions); inflammatory (thickening of the mucous membrane, opacity, polyp, mucosal retention cyst); systemic; and a quiet sinus [6, 8].

A new etiopathogenetic classification of iatrogenic maxillary sinusitis of stomatogenic origin makes it possible to differentiate individual forms of this disease by an iatrogenic causative factor [14]. The study of the state of the immune system, as one of the links in the pathogenesis of the disease, for rational therapy, depending on the cause and circumstances of the development of maxillary sinusitis, is justified. The nature of immune reconstructions in patients with sinusitis has been considered in a number of works, however, there are no data in the literature characterizing the degree of immune changes in patients with various forms of iatrogenic maxillary sinusitis.

The purpose of the study was to elucidate the severity of the course of various forms of stomatogenic maxillary sinusitis by studying the indicators of general immunity.

Materials and methods. A total 45 (100.0 %) patients, who were hospitalized in the Department of Surgical Dentistry and Maxillo-facial Surgery with severe clinical signs of exacerbation of inflammation in the maxillary sinus were included in this study. Into control group – odontogenic maxillary sinusitis (OMS), there were 7 (15.5 %) patients (mean age of 35.3±2.4 years) who had inflammation in the sinus developed from previously untreated teeth. Into the group of the infectious-allergic form of iatrogenic maxillary sinusitis (IAIMS) were added 9 (20.0 %) patients (mean age is 40.5±12.7 years) who had established a periapical infection of previously treated teeth in the sinus in the aetiology of the disease. The group of the mixed form of iatrogenic maxillary sinusitis (MixIMS) contained 11 (24.4 %) patients in the age of 40.2±14.0 with filling material or a fragment of the tooth root in the maxillary sinus. The group of medicamentous (drug) form (MedIMS) were included 5 (11.1 %) patients (mean age 57.6±4.5 years) who had maxillary sinusitis developed in the background of dental manipulations and the presence of concomitant chronic diseases accompanied by long reception of hormones, antibiotics or drugs. In the group of the traumatic form of iatrogenic maxillary sinusitis (TIMS) were included 13 (28.9 %) patients (in the age 43.8±14.0 in average) with sinusitis that developed against surgical manipulations in the area of the alveolar process or the body of the upper jaw [1].

All patients received antibacterial and anti-inflammatory therapy. To obtain information on the quantitative and qualitative composition of microbes, in the selected material, the «swab-loop» inoculation method was used. We were canceled antibiotics 24 hours before surgery. Isolates were identified on Vitek 2-compact (bioMérieux, France).

The immunity indices were determined by the method of immuno-enzymatic analysis and flow cytometry.

Data Processing. Statistical analysis was performed with Statistica Version 8.0 statistic software package. Data were expressed as means±standard deviation ((M±SD) or as median and interquartile range (Me[Q1; Q3]). Comparisons between groups were performed with analysis of as non-parametric as parametric test. Two independent groups were compared using the Mann-Whitney U test, three or more using the Kruskal-Wallis rank analysis of variations followed by pairwise comparison of groups using the Mann-Whitney test. The analysis of the difference in frequencies in two independent groups was carried out using Fisher's exact test with a two-sided confidence level, the χ^2 test with Yates' correction. Also, a t-test was used. The difference in values was considered statistically significant when $p<0.05$.

The study was approved by the Bioethics Commission of the State Institution "Institute of Dentistry and Oral and Facial Surgery of the National Academy of Medical Sciences of Ukraine", Odesa on 19.11.2020. All studies were carried out in accordance with the requirements of the Helsinki Patient Rights.

Patients with acute maxillary sinusitis, patients with a history of oncological diseases with tumour diseases, and patients with pansinusitis were excluded from the study.

Results of the study and their discussion. Gram-positive bacteria accounted for 60.0 % of the species diversity of the microbiota of the infectious – allergic group and only Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus were represented; gram-negative flora – Pseudomonas aeruginosa, Acinetobacter baumanni. In terms of the number of isolated strains, the first place was taken by gram-negative Acinetobacter baumanni, found in 30.7 % of the sinuses, which accounted for 40.0 % of all strains. Seeding of the sinuses with bacteria is within 10^3 CFU/ml in 50.0 % of cases, 10^7 CFU/ml – in 30.0 %, 10^4 CFU/ml – in 20.0 %.

In the affected sinuses of patients of the subgroup of the traumatic form of iatrogenic sinusitis, gram-positive cocci prevailed, constituting 41.7 % of the aerobic microflora and represented by S. aureus, S. epidermidis and S. Pluraminalium; Gram-negative bacilli accounted for 33.3 % of the aerobic flora and were represented by the species Klebsiella oxytoca, Klebsiella pneumonia and Escherichia coli. The fungi Candida Albicans and Cryptococcus laurentii accounted for 25.0 % of the microbiota. In the nasal sinuses, pathogens are present at a concentration of 10^7 CFU/ml in 50.0 % of cases, ($p=0.047$).

We inoculated only gram-positive bacteria: S. aureus, S. epidermidis, S. pneumoniae (80.0 %) and C. Albicans fungi (20.0 %) in the IAIMS subgroup. The maximum index of infection with pathogens was 10^5 CFU/ml, and was in 20.0 % of cases. The minimum index of infection was 10^3 CFU/ml – in 50.0 % of cases.

Gram-negative bacteria Moraxella catarrhalis and Klebsiella pneumonia prevailed in the microbiota of the MedIMS subgroup and accounted for 33.3 % of the seeded forms. Gram-positive flora was represented only by S. epidermidis (16.7 %), fungi – Candida Albicans and Candida kruzei (50.0 %). A wide variety of indicators of contamination of pathogens was noted from 10^3 CFU/ml to 10^7 CFU/ml. More often (in 26.6 % of cases) there was an index of contamination of 10^5 CFU/ml in Candida ablikans and Candida kruzei.

Aerobic flora, which was present in 71.4 % of patients with a MixIMS, 50.0 % consisted of S. aureus gram-positive cocci (p=0.01). Gram-negative bacilli accounted for 33.3 % of the microbiota and were represented by the species K. pneumonia and Hemophilus influenza, fungi – C. Albicans, accounted for 16.7 %. The maximum index of contamination in the maxillary sinuses of patients with a mixed form of iatrogenic sinusitis is 10^5 CFU/ml.

The concentration of cytotoxic T cells (CD 3+, CD56+) was relatively higher in the blood of patients from MedIMS subgroup (5.8 %); the relative minimum was found in the IAIMS subgroup (3.0 %), p=0.04. The values of cytotoxic cells (CD 3+, CD 56+) in the blood of patients of the subgroup MixIMS (4.0 %) significantly (p=0.02) differed from the indicator TIMS (4.5 %) and IAMS (3.0 %); and patients of TIMS (4.5 %) with patients of MedIMS subgroup (5.8 %), p=0.042. The values of other subpopulations of lymphocytes in the studied groups and subgroups were similar, their differences were insignificant (p=0.4).

A comparatively weak manifestation of the reaction of cellular immunity to bacterial invasion of the maxillary sinuses during their inflammation against the background of endodontic treatment in patients of the IAIMS subgroup is observed against the background of timely dental therapy. In the MedIMS subgroup, which is characterized by a long, sluggish, often asymptomatic course of chronic inflammation in the maxillary sinus while taking medications, the highest values of cytotoxic cells (5.8 %) were obtained, which indicated relatively greater severity of inflammatory processes in the sine (fig. 1).

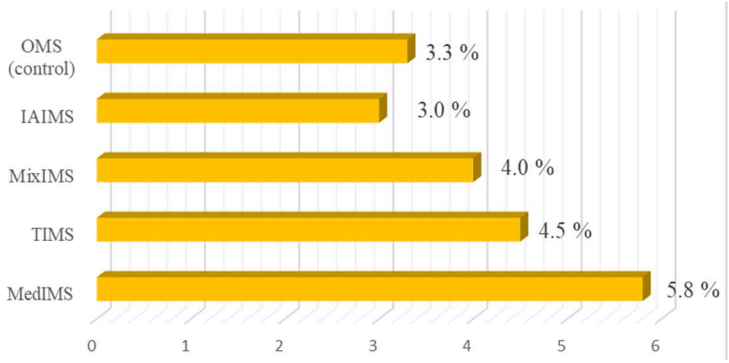

Fig. 1. The average value of cytotoxic T cells in the blood.

The smallest concentration of cytotoxic T cells (CD 3+, CD 56+) in the IAIMS group and medium immunocirculatory complexes in the OMS (control) group may be an indicators of a relatively mild course of the acute phase of chronic inflammation, which is consistent with the data of clinical and morphological studies. Relatively weak manifestations of the immune response were traced in low values of the average circulating immune complexes in the blood of patients with MedIMS (82.4±4.45 OU) relative to other subgroups of the main group (p>0.05) and the control group (93.9±1.82 OU), p=0.0001.

Analysis of the data of humoral immunity showed high mean IgA values (3.03±0.21 g/l) and IgG (15.27±3.47 g/l), in medicamentous (drug) form of iatrogenic maxillary sinusitis in comparison with the rest study groups. These values in the medicamentous group significantly differed from the values in the group of the mixed form of iatrogenic maxillary sinusitis – IgA (2.19±0.14 g/l) and IgG (9.14±0.6 g/l), p=0.00001.

The highest IgE was in the traumatic form of iatrogenic sinusitis 226.16±70.4 IU/ml, the second largest indicator was in the medicamentous (drug) form of iatrogenic sinusitis 173.38±76.71 IU/ml, p=0.02. In the group with odontogenic sinusitis (control), the concentration of serum IgE was 136.95±71.48 IU/ml, in the subgroup of medicamentous (drug) form – 85.26±58.49 IU/ml (p=0.21); in the subgroup with mixed form of iatrogenic maxillary sinusitis – 32.32±8.83 IU/ml significantly lesser than in the group of traumatic 226.16±70.4 IU/ml) iatrogenic sinusitis (p=0.000001).

U test (Mann-Whitney test) was performed to determine if the differences in the level of circulating immune complexes in the blood of patients with various forms of stomatologic maxillary sinusitis is statistically significant. The analysis results are shown in table 1.

Table 1

Differences in the immune response of patients with different forms of stomatologic maxillary sinusitis based on level of circulating immune complexes in the blood (Me [Q1;Q3], %)

Investigated immunity indices		Odontogen maxillar sinusit (control) n=7	Iatrogenic group of maxillar sinusit			
			Traumatic form n=13	Mixed form n=11	Medicamentous (drug) form n=5	Infectious-allergic form n=9
major (OU)	Me [Q_1;Q_3]	7.0 [4.0;10.0]	6.0 [4.0;9.0]	6.0 [4.0;11.0]	6.0 [5.0;8.0]	6.0 [4.0;9.0]
	P	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05
medium (OU)	Me [Q_1;Q_3]	94.0 [88.0;98.0]	93,0 [82.0;94.0]	81.0 [77.0;89.0]	81,0 [73.0;90.0]	93.0 [82.0;94.0]
	P	p^*<0.05	p>0.05	p>0.05	p^*<0.05	p>0.05
small (OU)	Me [Q_1;Q_3]	177.0 [171;183]	173.0 [168;179]	171.0 [167;185]	175.0 [172;181]	173.0 [168;179]
	P	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05

* Observed differences between the comparing groups are statistically significant (p <0.05)

Significance of differences was noted only in the values to the medium circulating immune complexes (CIC) in the blood of the control group (94.0 [88.0; 98.0] OU) and in the drug-induced drug form of iatrogenic sinusitis (81 [73.0; 90.0] OU), p=0.038.

Thus, a careful analysis of the results of the study of the state of immunity in groups with the various forms of stomatogenical maxillary sinusitis showed that the average values of the majority of the data obtained in the groups are within the norm and have close values. Differences were found in the relative values of cytotoxic cells (CD3+, CD56+), IgA, IgG and IgE, as well as the average circulating immune complexes in the blood.

A severe immunodeficiency occurs as a result of dysfunction of T-cells, which are mainly involved in the body's defense against viral, bacterial and fungal infections. T cells also play an important role in the adaptive immune response and are closely involved in the recruitment and activation of B cells by stimulating antibody production. The degree of dysfunction of the immune system, being the basis of many diseases associated with the state of infection, can be an indicator of the depth of the course of the inflammatory process [12]. The highest concentrations of cytotoxic T cells (CD3+, CD56+) were in the group with the medicamentous (drug) (5.8 %), the low concentrations - infectious-allergic form of iatrogenic maxillary sinusitis (3.0 %), p<0.05. Thus, based on the data obtained, it can be argued that the treatment of the causative teeth has a beneficial effect on the course of sinusitis, and the chronic use of antibiotics, hormones or drugs has a negative effect.

Also, the mean circulating immune complexes in the blood in the group of the medicamentous (drug) form of iatrogenic sinusitis (82.4±4.45 OU) were lower than in the other iatrogenic sinusitis groups, p>0.05 and significantly lower than in the control (93.9±1.82 OU) p=0.0001. It confirms a relatively weak manifestation of acute inflammation in group with medicamentous (drug) sinusitis.

The function of protecting the mucous membranes is performed by secretory IgA, which, by binding to bacteria, prevents their adhesion to the mucosal surface. Its increase can be regarded as a switch of the primary immune response to the secondary. An increase in IgM should be considered as the primary immune response to an infectious agent. As for IgG, with a normal immune response, it assumes the main part of the protective function in neutralizing the antigen. A sharp rise in immunoglobulin G can be a criterion for the strength of the immune system and a violation of the local defense mechanism [3].

IgE and its functions are at the heart of the therapeutic effort for allergy treatment. The pathogenic role of immunoglobulin E (IgE) antibodies in triggering and maintaining allergic inflammation in response to allergens is due to the binding of multivalent allergens to allergen-specific IgE on sensitized effector cells. These interactions initiate the activation of effector cells, resulting in the release of potent inflammatory mediators, the recruitment of inflammatory cells, antigen presentation, and the production of allergen-specific antibodies [10].

CIC is able to stimulate the development of the body's immune response. As a rule, these complexes are quickly removed from the blood, but with prolonged exposure to antigens, the level of CIC in the blood increases. In addition, this increase occurs in diseases characterized by the development of autoimmune processes [9]. An important factor for the manifestation of the pathogenic properties of CICs is their size. Low molecular weight complexes are inferior to large complexes that activate complement [7]. Thus, by determining the size of the CIC, one can indirectly assess their biological properties and possible negative consequences. The greatest pathological potential is inherent in medium-sized soluble immune complexes formed with a slight excess of antigen, capable of activating complement. The detected

increase in the level of circulating immune complexes of small and medium size in the serum may indicate a predisposition of this category of patients to the development of immunopathological reactions [1].

Conclusion

The nature of iatrogenic affects the picture of microbiota of maxillary sinus and of general immunity in patients with maxillary sinusitis. In the drug-induced form of iatrogenic maxillary sinusitis, changes in the patient's immunological status are caused by taking medications for a long period of time; the nature of dental manipulations is a minor factor in the pathogenesis of the disease. In all other forms of iatrogenic maxillary sinusitis of stomatogenic origin, the mechanism of development and the severity of the disease directly depend on the nature and volume of dental intervention. For the drug (dosage) form of iatrogenic maxillary sinusitis, the acute phase of inflammation is relatively more pronounced. It was observed the level of indicators of T cells (CD 3+, CD 56+) (5.8 %), mean CIC (82.4±4.45 OU) $p<0.05$ and the secondary type of immune response - IgG (15.27±3.47 g/l) $p<0.05$ compare with low induced activity of immune cells (233.2±27.5 OU) of other investigated iatrogenic subgroups. For the traumatic form of iatrogenic maxillary sinusitis, primary sensitization is relatively pronounced – a high IgE value (226.16±70.4 IU/ml) $p<0.05$; a relatively favorable immunological course is observed in infectious-allergic and mixed forms of iatrogenic maxillary sinusitis.

Further research should be aimed at developing therapy for certain forms of iatrogenic sinusitis, taking into account the characteristics of causal factors and pathogenesis.

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